Appendix 6 – Characteristics and safety data from the included studies

How safe are topical corticosteroids compared to emollient or vehicle?

Study ID *(Systematic review*)*	Study design and study duration *(Quality assessment)*	Intervention and comparator	Participants	Cutaneous adverse events	Systemic adverse events	Unspecified adverse events
Very potent topical corticosteroids						
Breneman 2003 [1] (unpublished) ***(Feldman 2005 [2] Nankervis [3])***	RCT 2 weeks treatment, then followed up for additional 2 weeks *Cochrane risk of bias tool: randomisation described, allocation concealment unclear, intention-to-treat unclear.*	**Intervention:** Clobetasol propionate 0.05% lotion (twice a day) **(n=96)** **Intervention:** Clobetasol propionate 0.05% emollient cream (twice a day) (n=100) **Comparator:** Vehicle (n=33)	**Severity:** moderate to severe **Age:** ≥ 12 years **Sample size:** 229 participants	**Local application site skin reactions** No clinically significant telangiectasia or skin thinning		**Unspecified adverse events** Incidence comparable between groups. **Treatment-related adverse events** **Clobetasol lotion** = 4/96 patients (4.2%); **Clobetasol cream** = 1/100 patients (1%) **Vehicle** = 6/33 patients (18.2%) *(Difference between groups: p= 0.0006[a])*
Kimball 2008 [4] (trial a) ***(Frangos 2008 [5])***	RCT Duration not specified in review *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Clobetasol propionate emulsion formulation foam 0.05% **Comparator:** Vehicle	**Severity:** not specified in the review **Age:** not specified in the review **Sample size:** not specified in the review			**Incidence of adverse events or treatment related adverse events** **Clobetasol foam** = 8% **Vehicle foam** = 10% *(no significant differences between groups)*
Rosso 2009 [6] ***(Barnes 2009 [7])***	RCT 2 weeks treatment *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Fluocinonide 0.1% cream (n=109) **Comparator:** Vehicle (n=50)	**Severity:** not specified in the review **Age:** not specified in the review **Sample size:** 159 participants	**Skin thinning** **Fluocinonide:** 6/109 participants (5.6%) **Vehicle:** 2/50 participants (4.3%) *(Difference between groups: p=0.69[a])*		
www.olux-e.com (online data) [8] ***(Frangos 2008 [5])***	Single arm study (observational) 2 weeks treatment	**Intervention:** Clobetasol propionate emollient foam (twice daily) (n=37) **Comparator:** No comparator	**Severity:** ≥30% BSA **Age:** ≥12 years old **Sample size:** 37 participants		**HPA axis suppression** 6/37 patients (16%) *(not specified in the review how it was measured)*	

	Risk of bias not assessed in any of the included systematic reviews.					
Kimball 2008 [4] (trial b) ***(Frangos 2008 [5]; Wood Heickman 2018 [9])***	Open label Phase II safety study 2 weeks treatment *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Clobetasol propionate emollient foam 0.05% (twice daily) (n=52) **Comparator:** No comparator	**Severity:** mild to severe **Age:** children (from 6 years old) and adults **Sample size:** 52 participants		**HPA axis suppression** 7/30 (23.3%) had adrenal insufficiency (ACTH stimulation testing, measuring serum cortisol levels). • 47% of children (aged 6-11) • 0% of adolescents (aged 12-17) • 27% of adults (≥18 years) Was reported as transient and reversible. After TCS discontinuation, children with biochemical adrenal insufficiency had complete resolution at retesting.	
Herz 1991 [10] ***(Barnes 2015 [7])***	Single arm study (observational) *(2 weeks treatment)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Clobetasol propionate (n=59) **Comparator:** No comparator	**Severity:** not specified in the review **Age:** not specified in the review **Sample size:** 59 participants	**Skin thinning** 1 case of skin thinning reported (not clear if in a psoriasis or eczema patient – but assume its eczema as this is the topic of the systematic review).		
Potent topical corticosteroids						
Sugarman 2009 [11] ***(Van Zuuren 2017 [12])***	RCT *(4 weeks treatment)* *(Cochrane risk of bias tool: low risk of selection, attrition and other biases. Unclear risk of reporting and performance bias, High risk of detection bias. [12])* *(Cochrane risk of bias tool: unclear risk of selection bias, high risk from no blinding. [3])*	**Intervention:** Fluticasone 0.05% cream twice daily (hydrocortisone 2.5% for the face and body folds) (n=62) **Comparator:** Ceramide-dominant barrier repair formulation (EpiCeram) twice daily (emollient) (n=59)	**Severity:** moderate to severe **Age:** children 6 months to 18 years (mean age 7.1 years) **Sample size:** 121 participants			**Serious adverse events** The participants did not report any in either group. No further details regarding other possible treatment related adverse events were reported.

Griffiths 2002 [13] ***(Nankervis 2017 [3])***	RCT *(up to 14 days treatment)* *(Cochrane risk of bias tool: low risk of selection bias from sequence generation, unclear risk of selection bias from allocation concealment, low risk from blinding. [3])*	**Intervention:** Hydrocortisone 17-butyrate cream (0.1%) maximum application of 2g (four fingertip units) per day (n=49) **Comparator:** Cipamfylline cream (1.5 mg of cipamfylline per gram of cream) used up to a maximum of 2 g (four fingertip units) of cream per day (emollient) (n=54)	**Severity:** not specified **Age:** adults ≥18 years old **Sample size:** 103 participants	No difference in cutaneous adverse events which were possibly or probably related to treatment in either group (p = 0.13) The adverse events were mostly application site reactions, including itching, stinging or burning, and drug reactions.		**Unspecified adverse events** **Hydrocortisone group:** 20/49 (40.8%) participants reported 41 adverse events in total. **Emollient:** 29/52 (55.8%) participants reported 63 adverse events in total. *(Difference between groups: p= 0.14 [a])*
Eichenfield 2006 [14] ***(Nankervis 2017 [3])***	RCT *(4 weeks treatment)* *Risk of bias not assessed*	**Intervention:** Fluticasone propionate four times daily (n=221) **Comparator:** Vehicle four times daily (n=217)	**Severity:** moderate to severe **Age:** children from 3 months old to 16 years old **Sample size:** 438 children			**Withdrawal due to adverse events** **Topical corticosteroids:** 4 participants in total from this study and from Hebert 2007 **The number of participants reporting at least 1 adverse event** **Fluticasone:** 77/221 (34.8%) participants **Vehicle:** 82/217 (37.8%) participants *(Difference between groups: p=0.52[a])*
Wu 2013 [15] ***(Nankervis 2017 [3], Fishbein 2019 [16])***	RCT *(10 days treatment)* *(Cochrane risk of bias tool: low risk of selection bias from sequence generation. Unclear risk of selection bias from allocation concealment, unclear risk from blinding and other biases: Two out of 60 participants were excluded from the analyses as they used concomitant medication [3])*	**Intervention:** Mometasone furoate 0.1% cream, twice a day (n=20) **Comparator:** placebo of distilled water in 1% dimethyl sulfoxide mixed with the identical cream base as used for the 15(R/S)-methyl-lipoxin A4 (n=20) **Comparator:** 15(R/S)-methyl-lipoxin A4 0.1% cream (n=20)	**Severity:** all severities **Age:** children from 1 month to 1 year old **Sample size:** 60 participants		None of the safety tests (e.g. full blood count, kidney and liver function test, and electrocardiogram) showed any significant differences compared with baseline for all three treatment groups.	No clinical adverse events were reported.

Pellanda 2005 [17] ***(Nankervis 2017 [3])***	RCT *(Duration not specified in the review)* *Risk of bias not assessed*	**Intervention:** Triamcinolone acetonide **Comparator:** Vehicle	**Severity:** mild to moderate **Age:** not specified in the review **Sample size:** not specified in the review	**Skin changes** One report by a participant using placebo (no further details)		
Lebwohl 1996 [18] ***(Hoare 2000 [19])***	RCT *(29 days treatment)* *(Moher 1995 quality checklist: method and concealment of randomisation unclear, double blinded, large number of withdrawals and dropouts, no ITT analysis [19])*	**Intervention:** Fluticasone propionate ointment 0.005% **Comparator:** Vehicle	**Severity:** not specified in the review **Age:** not specified in the review **Sample size:** 203 participants			The review authors only reported that *"Drug related adverse effects were rare"*
Lebwohl 1999 [20] ***(Hoare 2000 [19])***	RCT *(29 days treatment)* *(Moher 1995 quality checklist: method and concealment of randomisation unclear, double blinded, large number of withdrawals and dropouts, no ITT analysis [19])*	**Intervention:** Fluticasone propionate ointment 0.005% **Comparator:** Vehicle	**Severity:** not specified in the review **Age:** not specified in the review **Sample size:** 169 participants			The review authors only reported that *"Drug related adverse effects were rare"*
Abramovitis 2010 [21] ***(Wood Heickman 2018 [9], Fishbein 2019 [16])***	RCT (21 to 29 days treatment) *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Hydrocortisone butyrate 0.1% cream, twice daily (n=131) **Comparator:** Lipocream vehicle, twice daily (n=133)	**Severity:** Mild to moderate **Age:** children 3 months to 18 years (mean 7.2 years) **Sample size**: 264 children		**HPA axis suppression (no data for vehicle group)** 5/63 (7.9%) children in the hydrocortisone group (measured using ACTH stimulation testing, measuring serum cortisol levels) After TCS discontinuation, children with biochemical adrenal insufficiency had complete resolution at retesting.	**The number of participants reporting at least 1 adverse event** **Hydrocortisone:** 29/131 (22.1%) participants **Vehicle:** 28/133 (21.1%) participants *(Difference between groups: p=0.83 [a])*
Matheson 2008 [22]	RCT (28 days treatment)	**Intervention:** Hydrocortisone butyrate 0.1% lotion, twice daily (n=139)	**Severity:** Mild to moderate			**The number of participants reporting at least 1 adverse event** **Hydrocortisone:** 48/139 (34.5%)

(Fishbein 2019 [16])	*Risk of bias not assessed in any of the included systematic reviews.*	**Comparator:** Vehicle, twice daily (n=145)	**Age:** children 3 months to 18 years **Sample size**: 284 children			participants **Vehicle:** 56/145 (38.6%) participants *(Difference between groups: p=0.48 [a])*
Friedlander 2002 [23] ***(Callen 2007 [24]; Wood Heickman 2018 [9])***	Single arm study (observational) *(3 to 4 weeks)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Fluticasone propionate cream 0.05% (n=43) **Comparator:** No comparator	**Severity:** not specified in the review **Age:** children 3 months to 6 years **Sample size:** 43 participants		**HPA axis suppression** 2/43 (4.7%) children (measured using ACTH stimulation testing, measuring serum cortisol levels) After TCS discontinuation, children with biochemical adrenal insufficiency had complete resolution at retesting.	
Eichenfield 2007 [25] ***(Wood Heickman 2018 [9])***	Single arm study (observational) (4 weeks treatment) *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Hydrocortisone butyrate 0.1% (n=20) **Comparator:** No comparator	**Severity:** not specified in the review **Age:** children (median or mean = 9 years) **Sample size**: 20 children		**HPA axis suppression** 0/20 (0%) children (measured using ACTH stimulation testing, measuring serum cortisol levels)	
Hebert 2006 [26] ***(Wood Heickman 2018 [9])***	Single arm study (observational) (3 to 4 weeks treatment) *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Fluticasone propionate 0.05% lotion (n=42) **Comparator:** No comparator	**Severity:** not specified in the review **Age:** children (median or mean 2.6 years) **Sample size**: 42 children		**HPA axis suppression** 0/42 (0%) children (measured using ACTH stimulation testing, measuring serum cortisol levels)	
Moderate potency topical corticosteroids						
De Belilovsky 2011 [27] ***(Van Zuuren 2017 [12])***	RCT *(3 weeks treatment)* *(Cochrane risk of bias tool: low risk of selection, attrition, reporting and other biases. Unclear risk of performance bias.*	**Intervention:** Hydrocortisone butyric propionate 0.1% twice daily (n=40) **Comparator:** Stelatopia (2% sunflower oil, fatty acids, ceramides) twice daily (n=40)	**Severity:** mild to moderate **Age:** children 4 months to 4 years (mean age 2.3 years) **Sample size:** 80 participants			No participants reported adverse events

	High risk of detection bias. [12]) *(Cochrane risk of bias tool: unclear risk of selection bias and risk from blinding. [3])*					
Rosenthal 1980 [28] ***(Singh 2012 [29])***	RCT (*14 days treatment)* *(Delphi list: method of randomisation not described, allocation not concealed, blinded, no ITT analysis [29])*	**Intervention:** Clocortolone pivalate 0.1% cream (applied thrice daily) **Comparator:** Vehicle (applied thrice daily)	**Severity:** not specified in the review **Age:** not specified in the review **Sample size:** 100 participants			No adverse events
Binder 1977 [30] ***(Singh 2012 [29])***	RCT *(14 days treatment)* *(Delphi list: method of randomisation not described, allocation not concealed, blinded, no ITT analysis [29])*	**Intervention:** Clocortolone pivalate (applied thrice daily) (n=17) **Comparator:** Vehicle (n=12)	**Severity:** not specified in the review **Age:** mean age 30 years **Sample size:** 29 participants	**Irritation and dryness** Clinically significant in one patient in each group – did not result in discontinuation.		
Rauschkol 1981 [31] ***(Fishbein 2019 [16])***	Within-participant RCT *(14 days treatment)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Halcinonide 0.025% cream, twice daily, on one arm **Comparator:** Placebo cream unspecified, twice daily on the other arm at the same time	**Severity:** not reported **Age:** children 7 months to 15 years (mean age 8 years) **Sample size:** 86 children			**The number of participants reporting at least 1 adverse event** **Halcinonide:** 4/86 (4.7%) participants **Placebo:** 5/86 (5.8%) participants
Nolting 1991 [32] ***(De Tiedra 1997 [33])***	RCT (but safety data only presented for one arm) *(21 days treatment)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Prednicarbate cream 0.25% (2 applications per day) (n=34) **Comparator:** mometasone cream 0.1% twice daily (no safety data given)	**Severity:** Disease duration = mean 4.1 years ± 2.7 **Age:** children 2-12 years (mean 6.6 ± 3.6). **Sample size:** 34 participants (with safety data)			**Adverse reactions** 2/34 patients (5.9%)
Rampini 1992 [34]	RCT (but safety data only presented for one arm)	Intervention: Prednicarbate cream/unguent 0.25% (2 applications per day) (n=93)	**Severity:** not specified in the review			**Adverse reactions** 3/93 patients (3.2%)

(De Tiedra 1997 [33])	*(21 days treatment)* *(Moher 1995 quality checklist: method and concealment of randomisation unclear, double blinded, two dropouts, no ITT analysis, [19])*	Comparator:methylprednisolone aceponate 0.1% once daily (no safety data given)	**Age:** children 0.3 to 14 years (mean 6.6). **Sample size:** 93 participants (with safety data)			
Camacho 1996 [35] ***(De Tiedra 1997 [33])***	RCT (but safety data only presented for one arm) *(21 days treatment)* *(Moher 1995 quality checklist: method and concealment of randomisation unclear, double blinded, no ITT analysis, 14/49 dropouts, [19])*	**Intervention:** Prednicarbate cream 0.25% (2 applications per day) (n=49) **Comparator:** fluocortolone pivalate cream 0.2% (no safety data given)	**Severity:** Disease duration= mean 6.2 years ± 8.2 (range 0.25 to 39 years). **Age:** adults 19 to 65 years (mean 34.1 ± 12). **Sample size:** 49 participants (with safety data)			**Adverse reactions** 4/49 patients (8.1%)
Gimenez Camarasa 1994 [36] ***(De Tiedra 1997 [33])***	RCT (but safety data only presented for one arm) *(21 days treatment)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Prednicarbate cream 0.25% (2 applications per day) (n=41) **Comparator**: fluocinolone cream 0.025% twice daily (no safety data given)	**Severity:** Disease duration = mean 6.4 years ± 8.6 (range 0-40). **Age:** adults 18 to 77 years (mean 37.6 ± 15.9). **Sample size:** 41 participants (with safety data)			**Adverse reactions** 0/41 patients (0%)
Moshang 2001 [37] ***(Callen 2007 [24]; Wood Heickman 2018 [9])***	Single arm study (observational) *(3 weeks treatment)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Prednicarbate emollient cream 0.1%, twice daily (n=55) **Comparator:** No comparator	**Severity:** not specified in the review **Age:** children 4 months to 12 years **Sample size:** 55 participants		**HPA axis suppression** All normal (measured using ACTH stimulation testing, measuring serum cortisol levels)	
Conde 2008 [38] ***(Singh 2012 [29])***	Single arm study (observational) *(4 weeks treatment)*	**Intervention:** Clocortolone pivalate cream 0.1% twice daily (n=10) **Comparator:** No comparator	**Severity:** mild to moderate **Age:** children, mean age 7.9 years			No adverse events reported

	Risk of bias not assessed in any of the included systematic reviews.		**Sample size:** 10 participants			
Crespi 1986 [39] ***(Callen 2007 [24])***	Single arm study (observational) *(4 weeks treatment)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Alclometasone cream, twice daily (n=39) **Comparator:** No comparator	**Severity:** not specified in the review **Age:** children **Sample size:** 39 participants		**HPA axis suppression** All normal (measured via morning cortisol)	
Mild potency topical corticosteroids						
Udompataikul 2011 [40] ***(Van Zuuren 2017 [12])***	Within-participant RCT *(6 weeks treatment)* *(Cochrane risk of bias tool: unclear risk of selection, performance and attrition bias. Low risk of reporting and other biases. High risk of detection bias. [12])* *(Cochrane risk of bias tool: unclear risk of selection bias from sequence generation and risk from blinding. Low risk of selection bias from allocation concealment, [3])*	**Intervention:** Hydrocortisone acetate 1% cream twice daily, was applied one side of the body for 4 weeks followed by the cream base for 2 weeks. **Comparator:** Licochalcone (containing *Glycyrrhiza inflata* root extract, decanediol, menthoxypropanediol and 6-fatty acids) applied twice daily on one side of the body for 6 weeks	**Severity:** mild to moderate **Age:** children 2 months to 10 years (mean age 5.8 years) **Sample size:** 30 participants			No adverse events on either side during the study.
Hebert 2007 [41] ***(Nankervis 2017 [3], Fishbein 2019 [16])***	RCT *(28 days)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Desonide 0.05% gel twice daily (n=425) **Comparator:** Hydrogel vehicle twice daily (n=157)	**Severity:** mild to moderate **Age:** children 3 months to 18 years **Sample size:** 582 children			**Serious adverse events** One event reported in TCS group but not thought to be related to treatment **Withdrawal due to adverse events** TCS group: 4 in total from this study and from Eichenfield 2006 **The number of participants reporting at least 1 adverse event** **Desonide:** 85/425 (20 %) participants **Vehicle:** 46/157 (29.3%)

						participants *(Difference between groups: p=0.02 [a])*
Udompataikul 2012 [42] ***(Fishbein 2019 [16])***	Within-participant RCT *(4 weeks treatment)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Hydrocortisone 1% ointment twice daily, applied to one arm. **Comparator:** 5% dexapanthenol ointment twice daily, applied to the other arm at the same time.	**Severity:** mild to moderate **Age:** children 2 years to 15 years (mean age 7.2 years) **Sample size:** 30 participants			No adverse events on either side during the study.
Wananukul 2013 [43] ***(Van Zuuren 2017 [12])***	Within-participant RCT *(4 weeks treatment)* *(Cochrane risk of bias tool: low risk of selection bias from sequence generation, performance, detection, attrition, reporting and other biases. Unclear risk of selection bias from allocation concealment. [12])*	**Intervention:** Hydrocortisone acetate 1% cream twice daily on one side of the body **Comparator:** Licochalcone (containing *Glycyrrhiza inflata* root extract, decanediol, menthoxypropanediol and 6-fatty acids) twice daily on one side of the body	**Severity:** mild to moderate **Age:** children, mean age 3.1 years **Sample size:** 55 participants			No adverse events on either side during the study
Jirabundansuk 2014 [44] ***(Van Zuuren 2017 [12])***	Within-participant RCT *(4 weeks treatment)* *(Cochrane risk of bias tool: Unclear risk of selection and performance bias. High risk of detection bias. Low risk of attrition, reporting and other biases. [12])*	**Intervention:** Hydrocortisone acetate 1% cream twice daily on one side of the body **Comparator:** Moisturiser containing spent grain, Vitellaria paradoxa (formerly Butyrospermum parkii) extract plus Argania spinosa kernel oil twice daily on one side of the body	**Severity:** Mild or moderate **Age:** children 2-15 years (mean age 4.3 years) **Sample size:** 31 participants			The investigators stated that "no specific adverse events were reported".
Dolle 2010 [45] ***(Nankervis 2017 [3])***	Within-participant RCT *(3 weeks treatment)* *(Cochrane risk of bias tool: unclear risk of selection bias and risk from blinding. [3])*	**Intervention:** 1% hydrocortisone solution once daily for 1st week then twice daily up to 3 weeks **Comparator:** 6% miltefosine solution once daily for 1st week then twice daily up to 3 weeks	**Severity:** moderate to severe **Age:** adults (≥18 years old) **Sample size:** 16 participants	**<u>Local topical adverse events related to the treatment</u>** **Hydrocortisone:** 7/16 participants (44%) **Emollient:** 10/16 participants (63%) These adverse events included pruritus, burning, tingling and dry	No systemic adverse events	No withdrawals because of adverse events

				skin. Dry skin was seen only with emollient treatment.		
Patzelt-Wenczler 2000 [46] ***(Nankervis 2017 [3])***	Within-participant RCT *(2 weeks treatment)* *(Cochrane risk of bias tool: unclear risk of selection bias and high risk from no blinding. [3])*	**Intervention:** Hydrocortisone 0.5% twice daily **Comparator:** Kamillosan® cream, containing 2% ethanolic extract of chamomile flowers, twice daily (emollient) Comparator: Vehicle cream applied twice daily	**Severity:** at least moderate **Age:** not specified in the review **Sample size:** 72 participants			Three participants in the emollient group withdrew early because of intolerability.
Paller 2003 [47] ***(Nankervis 2017 [3])***	RCT *(2 weeks treatment)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Fluocinolone acetonide 0.01% twice daily (n=45) **Comparator:** Vehicle twice daily (n=49)	**Severity:** not specified in the review **Age:** children from 2 to 12 years old **Sample size:** 94 participants	**Mild hypopigmentation** Two participants out of 45 reported this event with fluocinolone (4.4%)		
Patel 1995 [48] ***(Callen 2007 [24])***	Single arm study (observational) *(3-10 years follow up)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** 1% Hydrocortisone ointment (n=14; 9/14 intermittently used moderate to high potency) **Comparator:** No comparator	**Severity:** not specified in the review **Age:** children 3.1 to 10.7 years **Sample size:** 14 participants		**HPA axis suppression** Plasma cortisol levels - no change in basal/peak levels but peaked earlier	
Dohil 2009 [49] (Wood Heickman 2018 [9])	Single arm study (observational) (4 weeks duration) *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** fluocinolone acetonide 0.01% **Comparator:** No comparator	**Severity:** not specified in the review **Age:** children (median or mean age 1.1 years) **Sample size:** 24 participants		**HPA axis suppression** No cases of adrenal insufficiency *(measured using ACTH stimulation testing, measuring serum cortisol levels)*	
Eichenfield 2007 [50] (Wood Heickman 2018 [9])	Single arm study (observational) (4 weeks duration) *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Desonide hydrogel 0.05% **Comparator:** No comparator	**Severity:** not specified in the review **Age:** children (median or mean age 3.3 years)		**HPA axis suppression** No cases of adrenal insufficiency *(measured using ACTH stimulation testing, measuring serum cortisol levels)*	

			Sample size: 34 participants			
Hebert 2008 [51] (Wood Heickman 2018 [9])	Single arm study (observational) (4 weeks duration) *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Desonide 0.05% foam **Comparator:** No comparator	**Severity:** not specified in the review **Age:** children (median or mean age 6.7 years) **Sample size:** 75 participants		**HPA axis suppression** Three out of 75 participants had adrenal insufficiency *(measured using ACTH stimulation testing, measuring serum cortisol levels)*	

How safe are topical corticosteroids compared to topical calcineurin inhibitors?

Study ID *(Systematic review*)*	Study design and study duration *(Quality assessment)*	Intervention and comparator	Participants	Cutaneous adverse events	Systemic adverse events	Unspecified adverse events
Potent topical corticosteroids						
Bieber 2007 [52] ***(Broeders 2016 [53])***	RCT *(up to 3 weeks treatment)* *(Jadad score 4/5 – risk from sequence generation and allocation concealment [53])* *(Cochrane risk of bias tool: unclear risk of selection bias and from blinding. [3])* *(Cochrane risk of bias tool: unclear risk of selection bias. Low risk of performance, detection, attrition, reporting and other biases. [54])*	**Intervention:** Methyl-prednisolone 0.1% (n=129) once daily in the evening to all affected body surface areas for a minimum of 2 weeks and a maximum of 3 weeks and cleared areas treated for an additional 7 days post clearance. Also applied a vehicle ointment in the morning to maintain blinding. **Comparator:** Tacrolimus 0.03% (n=136), applied twice daily, morning and evening, to all affected body surface areas for a minimum of 2 weeks and a maximum of 3 weeks and cleared areas treated for an additional 7 days post clearance.	**Severity:** severe to very severe **Age:** children 2 to 15 years old **Sample size:** 265 participants	**Adverse events related to treatment** **Methyl-prednisolone:** 0/129 participants (0%) **Tacrolimus:** 6/136 participants (4.4%) *(Difference between groups: p=0.09 [a, b])*		**Severe adverse events** **Methyl-prednisolone:** 0/129 participants (0%) **Tacrolimus:** 6/136 participants (4.4%) *(Difference between groups: p=0.09 [a, c])* **Adverse events requiring discontinuation** **Methyl-prednisolone:** 0/129 (0%) **Tacrolimus:** 4/136 (3%) *(Difference between groups: p=0.15 [a])*
Doss 2010 [55] ***(Broeders 2016 [53])***	RCT *(3 weeks treatment twice daily, plus 3 weeks follow up with once daily treatment)*	**Intervention:** Fluticasone 0.005% ointment applied twice daily to all affected areas except eyelids until clearance, up to 3 weeks. All participants who responded to treatment could apply treatment once a day to	**Severity:** moderate to severe **Age:** children 2 to 15 years old	**Adverse events related to treatment** **Fluticasone:** 45/239 participants (19%) **Tacrolimus:** 55/239 participants (23%)		**Severe adverse events** **Fluticasone:** 2/239 participants (0.8%) **Tacrolimus:** 1/239 participants (0.4%) *(Difference between groups: p=0.57 [a])*

	(Jadad score 5/5 – risk from allocation concealment [53]) *(Cochrane risk of bias tool: unclear risk of selection bias and from blinding. [3])* *(Cochrane risk of bias tool: Low risk of selection, performance, detection, attrition, reporting and other biases. [54])* *Cochrane risk of bias tool: low risk of selection, performance, attrition, reporting and other biases. Unclear risk of performance bias [56]).*	the remaining lesions for another 3 weeks (n=239) **Comparator:** Tacrolimus 0.03% ointment applied twice daily to all affected areas except eyelids until clearance, up to 3 weeks. All participants who responded to treatment could apply treatment once a day to the remaining lesions for another 3 weeks (n=239)	**Sample size:** 478 participants	*(Difference between groups: p=0.26[a])* **Skin burning** **Fluticasone:** 6/239 (2.5%) **Tacrolimus:** 18/237 (7.6%) *(Difference between groups: p=0.02[a])* **Pruritus** **Fluticasone:** 8/239 participants (3.3%) **Tacrolimus:** 10/237 participants (4.2%) *(Difference between groups: p=0.62[a])* **Skin infection** **Fluticasone:** 49/239 participants (21%) **Tacrolimus:** 44/239 participants (18%) *(Difference between groups: p=0.56[a])*		**Adverse events requiring discontinuation** **Fluticasone:** 6/239 participants (2.5%) **Tacrolimus:** 4/239 participants (1.7%) *(Difference between groups: p=0.53[a])*
Doss 2009 [57] ***(Broeders 2016 [53])***	RCT *(3 weeks of treatment – then for a further 3 weeks either stop treatment, once daily treatment or switch to other treatment twice daily)* *(Jadad score 5/5 – risk from allocation concealment [53])* *(Cochrane risk of bias tool: unclear risk of selection bias and low risk from blinding. [3])*	**Intervention:** Fluticasone 0.005% ointment twice daily on facial eczema lesions for 3 weeks or until clearance (n=279) **Comparator:** Tacrolimus 0.1% twice daily on facial eczema lesions for 3 weeks or until clearance (n=287) For 21 days after the initial 3 weeks, the participants could stop treatments if the facial lesions had cleared; stay on the same treatment once a day; or swap treatment using it twice daily (still blinded)	**Severity:** moderate to severe **Age:** adults **Sample size:** 566 participants	**Adverse events related to treatment** **Fluticasone:** 42/279 participants (15%) **Tacrolimus:** 75/287 participants (26%) *(Difference between groups: p=0.001[a])* **Skin burning** **Fluticasone:** 9/279 participants (3.2%) **Tacrolimus:** 47/287 participants (16.4%) *(Difference between groups: p<0.00001[a])* **Pruritus** **Fluticasone:** 9/279 participants (3.2%) **Tacrolimus:** 12/287 participants (4.2%) *(Difference between groups: p=0.55[a])*		**Severe adverse events** **Fluticasone:** 0/279 participants (0%) **Tacrolimus:** 1/287 participants (0.3%) *(Difference between groups: p=0.51[a]).* **Adverse events requiring discontinuation** **Fluticasone:** 8/279 participants (2.9%) **Tacrolimus:** 7/287 participants (2.4%) *(Difference between groups: p=0.75[a])*

Luger 2001 [58] ***(Broeders 2016 [53])***	RCT *(up to 3 weeks treatment)* *(Jadad score 3/5 – risk from sequence generation and allocation concealment [53])* *(Cochrane risk of bias tool: unclear risk of selection bias and unclear risk from blinding. [3])* *(Jadad scale: 3/5 [59])* *(Cochrane risk of bias tool: unclear risk of selection bias, adequate blinding, inadequate loss to follow up. [60])*	**Intervention:** Betamethasone valerate 0.1% applied twice daily on all affected areas except for the head and neck for up to 3 weeks or until complete clearance if this was sooner (n=42) **Comparator:** Pimecrolimus 1% applied twice daily on all affected areas except for the head and neck for up to 3 weeks or until complete clearance if this was sooner (n=45)	**Severity:** moderate **Age:** adults ≥ 18 years old **Sample size:** 87 participants	**Pruritus** **Betamethasone:** 5/42 participants (12%) **Pimecrolimus:** 14/45 participants (31%) *(Difference between groups: p=0.04 [a])* **Skin burning** **Betamethasone:** 4/42 participants (9.5%) **Pimecrolimus:** 22/45 participants (49%) *(Difference between groups: p=0.001 [a])*		**Adverse events requiring discontinuation** **Betamethasone:** 1/42 participants (2.4%) **Pimecrolimus:** 3/45 participants (6.7%) *(Difference between groups: p=0.36 [a])*
Luger 2004 [61] ***(Broeders 2016 [53])***	*RCT* *(52 weeks. Twice daily until clearance, restarted with flares)* *(Jadad score 3/5 – risk from sequence generation and allocation concealment [53])* *(Cochrane risk of bias tool: unclear risk of selection bias, low risk from blinding. [3])* *(Jadad scale: 3/5 [59])* *(Cochrane risk of bias tool: adequate allocation generation, unclear allocation concealment, adequate blinding, inadequate loss to follow up. [60])*	**Intervention:** Triamcinolone 0.1% (potent) and Hydrocortisone acetate 1% (face) (Mild potency) twice daily until complete clearance and itching had stopped, then treatment restarted if inflammation recurred (n=330) **Comparator:** Pimecrolimus 1% twice daily until complete clearance and itching had stopped, then treatment restarted if inflammation recurred (n=328)	**Severity:** moderate to severe **Age:** adults (age 18 to 79 years) **Sample size:** 658 participants	**Skin burning** **Triamcinolone + hydrocortisone:** 36/330 participants (11%) **Pimecrolimus:** 85/328 participants (26%) *(Difference between groups: p<0.00001 [a])* **Pruritus** **Triamcinolone + hydrocortisone:** 6/330 participants (1.8%) **Pimecrolimus:** 18/328 participants (5.5%) *(Difference between groups: p=0.02 [a])* **Skin thinning** **Triamcinolone + hydrocortisone:** 3/330 participants (0.9%) **Pimecrolimus:** 0/328 participants (0%) *(Difference between groups: p=20 [a])* **Skin infection** **Triamcinolone + hydrocortisone:** 80/330 participants (24%)		**Severe adverse events** **Triamcinolone + hydrocortisone:** 21/330 participants (6.4%) **Pimecrolimus:** 16/328 participants (4.9%) *(Difference between groups: p=0.41 [a])*

				Pimecrolimus: 69/328 participants (21%) *(Difference between groups: p=0.33 [a])*		
Mandelin 2010 (62) ***(Broeders 2016 (53))***	RCT *(52 weeks, as prescribed until 7 days after clearance, then restarted with flares)* *(Jadad score 3/5 – risk from sequence generation and allocation concealment, (53))* *(Cochrane risk of bias tool: unclear risk of selection bias, risk from no blinding. (3))*	**Intervention:** Hydrocortisone butyrate 0.1% ointment (potent) and Hydrocortisone acetate 1% ointment (face) (Mild potency) twice daily, as prescribed, for a flare until 7 days after clearance, as many times as required in 1 year (n=40) **Comparator:** Tacrolimus 0.1% ointment twice daily, as prescribed, for a flare until 7 days after clearance, as many times as required in 1 year (n=40)	**Severity:** moderate to severe **Age:** adults **Sample size:** 80 participants	**Skin thinning** **Hydrocortisone:** 2/40 participants (5%) **Tacrolimus:** 0/40 participants (0%) *(Difference between groups: p=0.29 [a])* **Skin infection** **Hydrocortisone:** 17/40 participants (43%) **Tacrolimus:** 26/40 participants (65%) *(Difference between groups: p=0.05 [a])*		**Severe adverse events** None in either group

Reitamo 2002 (I) [63] ***(Broeders 2016 [53]; Iskedjian 2004 [64])***	RCT *(3 weeks treatment)* *(Jadad score 4/5 – risk from allocation concealment [53])* *(Cochrane risk of bias tool: unclear risk of selection bias, unclear risk from blinding. [3])* *(Jadad scale: 5/5, [59])* *(Cochrane risk of bias tool: Low risk of selection, performance, detection, attrition, reporting and other biases. [54])* *(Cochrane risk of bias tool: adequate randomisation and allocation concealment, blinding and ITT analysis done. [65])*	**Intervention:** Hydrocortisone butyrate 0.1% twice daily for 3 weeks (n=186) **Comparator:** Tacrolimus 0.1% twice daily for 3 weeks (n=191) **Comparator:** Tacrolimus 0.03% twice daily for 3 weeks (arm not included in Broeders 2016 review) (n=193)	**Severity:** moderate to severe **Age:** adults (age 16 to 70 years) **Sample size: 571** participants	**<u>Skin burning</u>** **Hydrocortisone:** 24/186 participants (13%) **Tacrolimus 0.1%:** 113/191 participants (59%) *(Difference between groups: p<0.00001 [a])* **<u>Pruritus</u>** **Hydrocortisone:** 18/186 participants (9.7%) **Tacrolimus 0.1%:** 29/191 participants (15%) *(Difference between groups: p=0.11 [a])* **<u>Erythema at application site</u>** **Hydrocortisone:** 1/186 participants (0.5%) **Tacrolimus 0.1%:** 7/191 participants (3.7%) **Tacrolimus 0.03%:** 4/193 participants (2.1%) *(Difference between groups: tacrolimus 0.1% versus hydrocortisone: p=0.07 [a])* (*Difference between groups: tacrolimus 0.03% versus hydrocortisone: p=0.23 [a])*		**<u>Severe adverse events</u>** **Hydrocortisone:** 0/186 participants (0%) **Tacrolimus 0.1%:** 1/191 participants (0.5%) *(Difference between groups: p=0.51 [a])* **<u>Adverse events requiring discontinuation</u>** **Hydrocortisone:** 3/186 participants (1.6%) **Tacrolimus 0.1%:** 8/191 participants (4.2%) *(Difference between groups: p=0.15 [a])*

Reitamo 2005 [66] ***(Broeders 2016 [53])***	RCT *(26 weeks)* twice daily treatment until 7 days after clearance, then whenever a flare occurs) *(Jadad score 5/5; [53])* *(Cochrane risk of bias tool: unclear risk of selection bias,, low risk from blinding. [3])* *(Jadad scale: 5/5, [59])* *(Cochrane risk of bias tool: High risk of attrition bias. Low risk of selection, performance, detection, reporting and other biases. [54])* *(Cochrane risk of bias tool: unclear risk of selection bias, unclear if blinded, and unclear if ITT analysis used. [65])*	**Intervention:** Hydrocortisone butyrate 0.1%(potent) **and** Hydrocortisone acetate 1% (face) (Mild potency) twice daily until 7 days after clearance of eczema each time a flare of eczema occurred for 6 months (n=485) **Comparator:** Tacrolimus 0.1% twice daily until 7 days after clearance of eczema each time a flare of eczema occurred for 6 months (n=487)	**Severity:** moderate to severe **Age:** adults (≥18 years old) **Sample size:** 972 participants	**Adverse events related to treatment** **Hydrocortisone:** 11/485 participants (2.3%) **Tacrolimus:** 7/487 participants (1.4%) *(Difference between groups: p=0.34[a])* **Skin burning** **Hydrocortisone:** 67/485 participants (14%) **Tacrolimus:** 255/487 participants (52%) *(Difference between groups: p<0.00001[a])* **Pruritus** **Hydrocortisone:** 65/485 participants (13%) **Tacrolimus:** 88/487 participants (18%) *(Difference between groups: p=0.05[a])* **Adverse events requiring discontinuation** **Hydrocortisone:** 16/485 participants (3.3%) **Tacrolimus:** 10/487 participants (2%) *(Difference between groups: p=0.23[a])* **Skin thinning** **Hydrocortisone:** 2/485 participants (0.4%) **Tacrolimus:** 0/487 participants (0%) *(Difference between groups: p=0.30[a])* **Skin infection** **Hydrocortisone:** 9/485 participants (1.9%) **Tacrolimus:** 13/487 participants (2.7%) *(Difference between groups: p=0.40[a])*		**Severe adverse events** **Hydrocortisone:** 9/485 participants (1.9%) **Tacrolimus:** 5/487 participants (1%) *(Difference between groups: p=0.29[a])* **Adverse events requiring discontinuation** **Hydrocortisone:** 16/485 participants (3.3%) **Tacrolimus:** 10/487 participants (2.1%) *(Difference between groups: p=0.23[a])*

Gradman 2007 [67] ***(Svensson 2016 [68]1)***	Crossover RCT *(2 weeks treatment)* *(Cochrane risk of bias tool: low risk of selection bias from sequence generation, but unclear for allocation concealment. Low risk from blinding. [3])*	**Intervention:** Mometasone furoate 0.1% once daily **Comparator:** Tacrolimus 0.1% twice daily	**Severity:** mild to moderate **Age:** children 5 to 12 years **Sample size:** 20 participants			**Withdrawal from study** **Mometasone:** 1 patient **Tacrolimus**: 1 patient
Kawashima 1997 [69] (Ashcroft 2005 [59])	RCT *(3 weeks treatment)* *(Jadad scale: 5/5, [59])*	**Intervention:** Betamethasone valerate 0.12% twice daily for three weeks (n=89) **Comparator:** tacrolimus 0.1% twice daily for three weeks (n=92)	**Severity:** mild to moderate **Age:** adults **Sample size:** 181 participants	**Skin infections** **Betamethasone:** 5/89 participants **Tacrolimus:** 6/92 participants (*Difference between groups: p=0.80[a])* **Skin burning** **Betamethasone:** 3/89 participants **Tacrolimus:** 25/92 participants (*Difference between groups: p=0.0004[a])*		
Potent or mild potency topical corticosteroids						
Hofman 2006 [70] ***(Broeders 2016 [53]; Siegfried 2016 [71])***	RCT *(2 weeks treatment, 28 weeks follow up)* *(Jadad score 5/5 – risk from sequence generation and allocation concealment [53])*	**Intervention:** Hydrocortisone ointment 1% (mild potency) twice daily for head/neck and hydrocortisone butyrate ointment 0.1% (potent) for trunk and limbs for 2 weeks then hydrocortisone 1% (mild potency) twice daily for flares. (n=124) **Comparator:** Tacrolimus 0.03% twice daily for 3 weeks then tacrolimus once daily and vehicle once daily for flares (n=133)	**Severity:** moderate to severe **Age:** children 2 to 11 years old (mean 6 years old) **Sample size:** 257 participants	**Adverse events related to treatment** **Hydrocortisone:** 2/124 participants (1.6%) **Tacrolimus:** 10/133 participants (7.5%) *(Difference between groups: p=0.04[a])* **Skin burning** **Hydrocortisone:** 0/124 participants (0%) **Tacrolimus:** 2/133 participants (1.5%) *(Difference between groups: p=0.32[a])* **Pruritus** **Hydrocortisone:** 4/124 participants (3%) **Tacrolimus:** 8/133 participants (6%)		**Severe adverse events** **Hydrocortisone:** 0/124 participants (0%) **Tacrolimus:** 2/133 participants (1.5%) (*Difference between groups: p=0.32[a])*

				(Difference between groups: p=0.30[a]) **Skin infection** **Hydrocortisone:** 4/124 participants (3.2%) **Tacrolimus:** 2/133 participants (1.5%) *(Difference between groups: p=0.37[a])* **Bacterial infection** **Hydrocortisone:** 3/124 participants (2%) **Tacrolimus:** 33/133 participants (2%) *(Difference between groups: p<0.0001)* **Viral infection** **Hydrocortisone:** incidence not reported **Tacrolimus:** 1/133 participants (0.8%)		
Moderate potency topical corticosteroids						
Sikder 2005 [72] ***(Broeders 2016 [53])***	RCT *(4 weeks treatment)* *(Jadad score 2/5 – risk from sequence generation and allocation concealment, no blinding of observer or patients, [53])* *(Cochrane risk of bias tool: Unclear risk of selection and detection bias. Low risk of performance, attrition, reporting and other biases.[54])* *(Cochrane risk of bias tool: low risk of selection bias, from blinding of participants and missing data. Unclear risk from*	**Intervention:** Clobetasone 0.05% twice daily (n=15) Tacrolimus 0.03% twice daily (n=15)	**Severity:** moderate to severe **Age:** children 7 to 15 years old **Sample size:** 30 participants	**Skin burning** **Clobetasone:** 1/15 participants (6.7%) **Tacrolimus**: 7/15 participants (47%) *(Difference between groups: p=0.05[a, d])* **Pruritus** **Clobetasone:** 2/15 participants (13%) **Tacrolimus**: 3/15 participants (20%) *(Difference between groups: p=0.63[a])*		

	blinding outcome assessors, reporting and other biases [56]).					
Torok 2003 [73] ***(Svensson 2011 [68])***	RCT *(3 weeks treatment)* *(Delphi list: method of randomisation not described, allocation not concealed, blinded assessors but not participants, ITT analysis, [29])*	**Intervention:** Clocortolone pivalate 0.1% twice daily (n=19) **Intervention:** Clocortolone 0.1% + Tacrolimus 0.1% twice daily (n=19) **Comparator:** Tacrolimus 0.1% twice daily (n=19)	**Severity:** not specified in the review **Age:** adults 16 to 65 years **Sample size:** 57 participants	**Skin irritation** Most commonly reported adverse event **Skin burning** More frequent in those treated with Tacrolimus 0.1%. **Pruritus** Commonly reported in both arms. *(No numerical data provided in the review)*		
Moderate or mild potency topical corticosteroids						
Sigurgeirsson 2015 [74] ***(Broeders 2016 [53]; Siegfried 2016 [71])***	RCT *(260 weeks used until clearance or according to country's label. Medication reinstated when a flare occurred)*) *(Jadad score 3/5 – risk from allocation concealment, no blinding of observer or patients, [53])*	**Intervention:** A moderate potency or mild potency TCS used according to the country's label with potency selected by the investigator (n=1213) **Comparator:** Pimecrolimus 1% twice daily (n=1205)	**Severity:** mild to moderate **Age:** children age 3 to 12 months old (mean 7 months) **Sample size:** 2418 participants	**Skin thinning*(from online correspondence)*** **Topical corticosteroid:** 1/1213 participants (0.08%) **Pimecrolimus:** 0/1205 (0%) *(Difference between groups: p=0.50[a])* **Skin infection** **Topical corticosteroid:** 150/1213 participants (12%) **Pimecrolimus:** 157/1205 participants (13%) *(Difference between groups: p=0.62[a])* **Cutaneous bacterial infection** **Topical corticosteroid:** 121/1213 participants (10%) **Pimecrolimus:** 145/1205 participants (12%) *(Difference between groups: p=0.11[a])* **Cutaneous viral infection** **Topical corticosteroid:** 279/1213 participants (23%) **Pimecrolimus:** 301/12 05 participants (25%)	**Systemic bacterial infection** **Topical corticosteroid:** 206/1213 participants (17%) **Pimecrolimus:** 205/1205 participants (17%) *(Difference between groups: p=0.98[a])* **Systemic viral infection** **Topical corticosteroid:** 206/1213 participants (17%) **Pimecrolimus:** 205/1205 participants (17%) *(Difference between groups: p=0.98[a])* **Systemic RTI** **Topical corticosteroid:** 388/1213 participants (32%) **Pimecrolimus:** 422/1205 participants (35%) *(Difference between groups: p=0.11[a])* **Systemic GI** **Topical corticosteroid:** 376/1213 participants (31%) **Pimecrolimus:** 386/1205 participants (32%)	**Severe adverse events** **Topical corticosteroid:** 210/1213 participants (17%) **Pimecrolimus:** 247/1205 participants (20%) *(Difference between groups: p=0.05[a])* **Adverse events requiring discontinuation** **Topical corticosteroid:** 12/1213 participants (1.0%) **Pimecrolimus:** 7/1205 participants (0.6%) *(Difference between groups: p=0.26[a])*

				(Difference between groups: p=0.25[a])	*(Difference between groups: p=0.58[a])* **Lymphoma** Zero cases in either group **Growth rate and immune system** No difference between groups	
Mild potency topical corticosteroids						
Reitamo 2002 (II) [75] ***(Broeders 2016 [53]; Iskedjian 2004 [64])***	RCT *(3 weeks treatment)* *(Jadad score 5/5 – risk from allocation concealment [53])* *(Cochrane risk of bias tool: unclear risk of selection bias, unclear risk of blinding [3])* *(Jadad scale: 5/5, [59])* *(Cochrane risk of bias tool: Low risk of selection, performance, detection, attrition, reporting and other biases. [54])* *Cochrane risk of bias tool: low risk of selection, performance, attrition, reporting and other bias. Unclear risk from blinding outcome assessors [56]).* *(Cochrane risk of bias tool: adequate method of randomisation and allocation concealment, blinding done, ITT used. [65])*	**Intervention:** Hydrocortisone acetate 1% twice daily (n=185) **Comparator:** Tacrolimus 0.1% ointment twice daily (n=186) **Comparator:** Tacrolimus 0.03% ointment twice daily (arm not included in Broeders 2016 review) (n=189)	**Severity:** moderate to severe **Age:** children 2 to 15 years old **Sample size:** 560participants	**Skin burning** **Hydrocortisone:** 13/185 participants (7%) **Tacrolimus 0.1%:** 38/186 participants (20%) *(Difference between groups: p=0.004[a])* **Pruritus** **Hydrocortisone:** 14/185 participants (7.6%) **Tacrolimus 0.1%:** 21/186 participants (11%) *(Difference between groups: p=0.22[a])* **Skin infection** **Hydrocortisone:** 4/185 participants (2.2%) **Tacrolimus 0.1%:** 4/186 participants (2.2%) *(Difference between groups: p=0.99[a])* **Erythema at application site** **Hydrocortisone:** 3/185 participants (1.6%) **Tacrolimus 0.1%:** 1/186 participants (0.5%) **Tacrolimus 0.03%:** 4/189 participants (2.1%) *(Difference between groups, hydrocortisone vs tacrolimus 0.1%: P=0.34[a])* *(Difference between groups, hydrocortisone vs tacrolimus 0.03%: P=0.72[a])*		**Severe adverse events** **Hydrocortisone:** 2/185 participants (1.1%) **Tacrolimus 0.1%:** 1/186 participants (0.5%) *(Difference between groups: (p=0.57[a])* **Adverse events requiring discontinuation** **Hydrocortisone:** 4/185 participants (2.2%) **Tacrolimus 0.1%:** 3/186 participants (1.6%) *(Difference between groups: p=0.70[a])*

Reitamo 2004 (76) ***(Broeders 2016 (53))***	RCT *(3 weeks treatment)* *(Jadad score 3/5 – risk from sequence generation and allocation concealment (53))* *(Cochrane risk of bias tool: unclear risk of selection bias. Unclear risk from blinding. (3))* *(Jadad scale: 4/5, (59))* *(Cochrane risk of bias tool: Unclear risk of selection bias (allocation concealment). Low risk of selection bias (random sequence generation), performance, detection, attrition, reporting and other biases. (54))* *Cochrane risk of bias tool: low risk of selection, performance, attrition, reporting and other bias. Unclear risk from blinding outcome assessors (56)).*	**Intervention:** Hydrocortisone acetate 1% twice daily (n=207) **Comparator:** Tacrolimus 0.03% twice daily (n=210)	**Severity:** moderate to severe **Age:** children 2 to 15 years old **Sample size:** 417 participants	**Skin burning** **Hydrocortisone:** 30/207 participants (15%) **Tacrolimus:** 50/210 participants (24%) *(Difference between groups: p=0.02 [a])* **Pruritus** **Hydrocortisone:** 33/207 participants (16%) **Tacrolimus:** 45/210 participants (21%) *(Difference between groups: p=0.15 [a])* **Skin infection** **Hydrocortisone:** 6/207 participants (2.9%) **Tacrolimus:** 6/210 participants (2.9%) *(Difference between groups: p=0.98 [a])*		**Severe adverse events** **Hydrocortisone:** 3/207 participants (1.4%) **Tacrolimus:** 3/210 participants (1.4%) *(Difference between groups: p=0.99 [a])* **Adverse events requiring discontinuation** **Hydrocortisone:** 6/207 participants (2.9%) **Tacrolimus:** 8/210 participants (3.8%) *(Difference between groups: p=0.61 [a])*
Potency of topical corticosteroids unknown						
Gutgesell 1998 (77) (abstract only) ***(Penaloza Hidalgo 2004 (65))***	Within-participant RCT *(3 weeks treatment)* *(Cochrane risk of bias tool: randomisation and allocation concealment method inadequate, unclear if blinded ,ITT analysis used (65))*	**Intervention:** Topical corticosteroids on one side of the body, twice daily **Comparator:** Tacrolimus 0.1% on one side of the body, twice daily	**Severity:** severe **Age:** adults (22 to 36 years) **Sample size:** 7 participants	**Skin burning** **Topical corticosteroids:** 0/7 (0%) **Tacrolimus:** 2/7 participants (29%)		
Arellano 2007 (78) ***(Ashcroft 2007 (60));*** Cury Martins 2015 (54)	Nested case-control *(Duration not specified in the review)*	**Intervention:** Topical corticosteroids at different potencies **Comparator:** pimecrolimus or tacrolimus	**Severity:** not specified in the review **Age:** not specified in the review		**Lymphoma** No increased risk of lymphoma with TCI or TCS when compared against controls. ***Super potent TCS:*** OR 1.2, 95% CI 0.8 to 1.8	

	Risk of bias not assessed in any of the included systematic reviews.	**Comparator:** controls (not specified in the review)	**Sample size:** 294 cases/293,000 controls		***Low potency TCS:*** *OR* 1.1, 95%CI 0.7 to 1.6 ***Pimecrolimus:*** OR 0.8, 95%CI 0.4 to 1.6 ***Tacrolimus*** OR 0.8, 95% CI 0.4 to 1.7	
Arellano 2009 (79) (Cury Martins 2015 (54))	Cohort *(followed up between 1992 to 2006)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Topical corticosteroids at different potencies **Comparator:** pimecrolimus or tacrolimus	**Severity:** not specified in the review **Age:** not specified in the review **Sample size:** > 3,000,000		**Lymphoma** Increased risk with topical corticosteroids (related to potency) but no numerical data given. Insufficient data to assess TCI-related risks.	
Schneeweiss 2009 (80) ***(Cury Martins 2015 (54))***	Cohort *(followed up between the years of 2002 to 2006)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention: mid to potent t**opical corticosteroids (n=1,043,025) **Comparator:** pimecrolimus (n=118,863) or tacrolimus (n=38,757) (also a comparison with untreated dermatitis (n=118,825) and general population (n=118,863) .)	**Severity:** not specified **Age:** median 1.3 years **Sample size:** 1,438,333 participants		**Lymphoma** Very small non-significant increased risk in TCI and TCS patients when compared with the general population, but with similar risks between the treatment groups	
Reitamo 2000 (81) ***(Cury Martins 2015 (54))***	Open label, single group *(6 to 12 months of treatment)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** No steroids (except prior to treatment) **Comparator:** Tacrolimus 0.1%	**Severity:** not specified in the review **Age:** adults **Sample size:** 316 participants	**Skin thinning** One participant had skin thinning when using TCS prior to treatment with tacrolimus – but this ameliorated after 6 months of treatment with tacrolimus.		
Is there any difference in safety of topical corticosteroids of different potencies?						
Study ID *(Systematic review*)*	**Study design and study duration *(Quality assessment)***	**Intervention and comparator**	**Participants**	**Cutaneous adverse events**	**Systemic adverse events**	**Unspecified adverse events**
Potent topical corticosteroid versus moderate potency topical corticosteroid						
Ulrich 1991 (82) ***(Hoare 2000 (19))***	RCT *(2 weeks treatment)* *(Moher 1995 quality checklist: method and*	**Intervention:** 0.05% halomethasone cream, twice daily (Assume potent)	**Severity:** not specified in the review			No adverse events

	concealment of randomisation unclear, concerns over subgroup analysis [19])	**Comparator:** 0.25% prednicarbate cream, twice daily (moderate potency)	**Age:** not specified in the review **Sample size:** 165 participants			
Smitt 1993 [83] ***(Callen 2007 [24])***	RCT *(3 weeks treatment)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Trimaconiolone acetonide 0.1%, twice daily (potent) **Comparator:** Alclomethasone cream, twice daily (moderate)	**Severity:** not specified in the review **Age:** children 1 to 15 years **Sample size:** 40 participants		**HPA axis suppression** There was suppression after 2 weeks, but no further after 3 (no further details).	
Potent topical corticosteroid versus mild potency topical corticosteroid						
Lebrun-Vignes 2000 [84] ***(Nankervis 2017 [3])***	RCT *(15 days treatment, 30 days follow up)* *(Cochrane risk of bias tool: unclear risk of selection bias and unclear risk from blinding. [3])*	**Intervention:** Micronized desonide cream 0.1% (mild potency) 1 to 5 days twice daily (in hospital), days 6 and 7 once daily, then alternate days until day 15 (n=15) **Comparator:** Betamethasone dipropionate cream 0.05% (potent) 1 to 5 days twice daily (in hospital), days 6 and 7 once daily, then alternate days until day 15 (n=14)	**Severity:** severe **Age:** children ≤ 8 years **Sample size:** 29 participants			There were no adverse events in either group
Prado de Oliveira 2002 [85] ***(Nankervis 2017 [3])***	RCT *(Up to 42 days treatment)* *(Cochrane risk of bias tool: unclear risk of selection bias and unclear risk from blinding. [3])*	**Intervention:** Mometasone furoate 0.1% once daily after a bath (N=13) (potent) **Comparator:** Desonide cream 0.05% once a day after a bath (N=12) (mild potency)	**Severity:** not specified in the review **Age:** children 2 to 12 years **Sample size:** 25 participants	**Signs of mild thinning** **Mometasone furoate:** 4/13 participants (31%) **Desonide:** 2/12 participants (17%) *(Difference between groups: p=0.42 [a])*		
Hanifin 1996 [86] ***(Callen 2007 [24])***	Matched case control *(3 weeks treatment)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Mometasone cream (potent) **Comparator:** Hydrocortisone cream (mild potency)	**Severity:** not specified in the review **Age:** children 6 months to 2 years **Sample size:** 62 participants		**HPA axis suppression** **Mometasone:** 1 abnormal cotrosyn simulation test	

Kirkup 2003 [87] (trial a) ***(Tang 2014 [88]; Siegfried 2016 [71])*** Most safety data presented was combined with Kirkup 2003 (trial b) (see same potency section below)	RCT *(16 weeks: twice daily for 2-4 weeks until stabilised then 'as required' for 12 weeks)* *(Cochrane risk of bias tool: unclear risk of selection bias, unclear risk from blinding. [3])*	**Intervention:** Fluticasone propionate 0.005% ointment (potent), twice daily for 2-4 weeks until stabilised then 'as required' for 12 weeks (n=70) **Comparator:** Hydrocortisone 1% cream (mild potency), twice daily for 2-4 weeks until stabilised then 'as required' for 12 weeks (n=67)	**Severity: moderate** **Age:** children (age 2-14 years old) **Sample size (maintenance phase):** 137 participants	**Ringworm and folliculitis** 1 participant but not clear which group **Kirkup 2003a and b: Bacterial infection** **Fluticasone:** 1/136 participants (0.7%) **Hydrocortisone:** 3/129 participants (2%) *(Difference between groups: p = 0.32 [a])* **Kirkup 2003a and b: Fungal infection** **Fluticasone:** 1/136 participants (0.7%) **Hydrocortisone:** 0/129 (0%) *(Difference between groups: p = 0.52 [a])*	**Kirkup 2003a and b viral infection** **Fluticasone:** 5/136 participants (4%) **Hydrocortisone:** 5/129 participants (4%) *(Difference between groups: p = 0.93 [a])* **Kirkup 2003a and b: Respiratory tract infection** **Fluticasone:** 8/136 participants (6%) **Hydrocortisone**: 5/129 participants (4%) *(Difference between groups: p = 0.45 [a])*	**Kirkup 2003a and b: Discontinuation due to adverse events** **Fluticasone:** 1/136 participants (0.7%) **Hydrocortisone:** 1/129 participants (0.7%) *(Difference between groups: p = 0.97 [a])*
Moderate potency topical corticosteroid versus mild potency topical corticosteroid						
Kuokkanen 1987 [89] ***(Hoare 2000 [19])***	RCT, within participant *(3 weeks treatment)* *(Moher 1995 quality checklist: method and concealment of randomisation unclear, double blinded study, three dropouts/ withdrawals, no ITT, [19])*	**Intervention:** Alclometasone dipropionate 0.05% twice daily (moderate potency) **Comparator:** Hydrocortisone 1% twice daily (mild potency)	**Severity:** not specified in the review **Age:** children **Sample size:** 37 participants	No evidence of skin thinning		
Various potencies						
Ellison 2000 [90] ***(Callen 2007 [24]; Eichenfield 2014 [91])***	Observational study *(Duration 0.7 to 18.7 years)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Mild, moderate, potent topical corticosteroids	**Severity:** Disease severity score 5-8 **Age:** children and adolescents (0.7 to 18.7 years) **Sample size:** 35 participants		**HPA axis suppression** **Mild potency topical corticosteroids:** no change in plasma cortisol levels **Potent topical corticosteroids:** suppression in 4/4 (100%) patients	

Kristmundsdottir 1987 [92] ***(Eichenfield 2014 [91])***	Observational study *(Duration not specified in the review)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Different potencies of topical corticosteroids	**Severity:** not specified in the review **Age:** not specified in the review **Sample size:** not specified in the review		Review authors reported "Also concerns for negative effects on linear growth, although reports have given mixed conclusions"	
Patel 1997 [93] ***(Eichenfield 2014 [91])***	Observational study *(Duration not specified in the review)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Four different potency topical corticosteroids	**Severity:** not specified in the review **Age:** not specified in the review **Sample size:** not specified in the review		Review authors reported "Also concerns for negative effects on linear growth, although reports have given mixed conclusions"	
Patel 1998 [94] ***(Eichenfield 2014 [91])***	Observational study *(Duration not specified in the review)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Different potencies of topical corticosteroids	**Severity:** not specified in the review **Age:** not specified in the review **Sample size:** not specified in the review		Review authors reported "Also concerns for negative effects on linear growth, although reports have given mixed conclusions"	
Is there any difference in safety between topical corticosteroids of the same potency?						
Study ID *(Systematic review*)*	**Study design and study duration *(Quality assessment)***	**Intervention and comparator**	**Participants**	**Cutaneous adverse events**	**Systemic adverse events**	**Unspecified adverse events**
Potent topical corticosteroid versus another potent topical corticosteroid						
Kirkup 2003 [87] (trial b) ***(Tang 2014 [88]; Siegfried 2016 [71])*** Most safety data presented was combined with Kirkup 2003	RCT *(16 weeks: twice daily for 2-4 weeks until stabilised then intermittently for 12 weeks)* *(Cochrane risk of bias tool: unclear risk of selection bias, unclear risk from blinding. [3])*	**Intervention:** Fluticasone propionate 0.005% ointment, twice daily for 2-4 weeks until stabilised then intermittently for 12 weeks (n=66) **Comparator:** Hydrocortisone butyrate 0.1% cream (potent), twice daily for 2-4 weeks until	**Severity:** moderate **Age:** children (age 2-14 years old) **Sample size:** n=128	**Ringworm and folliculitis** None reported **Kirkup 2003a and b: Bacterial infection** **Fluticasone:** 1/136 participants (0.7%) **Hydrocortisone:** 3/129 participants (2%)	**Kirkup 2003a and b viral infection** **Fluticasone:** 5/136 participants (4%) **Hydrocortisone:** 5/129 participants (4%) *(Difference between groups: p = 0.93[a])* **Kirkup 2003a and b: Respiratory tract infection**	**Kirkup 2003a and b: Discontinuation due to adverse events** **Fluticasone:** 1/136 participants (0.7%) **Hydrocortisone:** 1/129 participants (0.7%) *(Difference between groups: p = 0.97[a])*

(trial a) (see different potency section above)		stabilised then intermittently for 12 weeks (n=62)		*(Difference between groups: p = 0.32 [a])* **<u>Kirkup 2003a and b: Fungal infection</u>** **Fluticasone:** 1/136 participants (0.7%) **Hydrocortisone:** 0/129 (0%) *(Difference between groups: p = 0.52 [a])*	**Fluticasone:** 8/136 participants (6%) **Hydrocortisone**: 5/129 participants (4%) *(Difference between groups: p = 0.45 [a])*	
Moderate potency topical corticosteroid versus another moderate potency topical corticosteroid						
Aliaga 1994 [95] ***(De Tiedra 1997 [33])***	RCT *(21 days treatment)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Prednicarbate ointment 0.25%, twice daily (moderate potency) (n=36) **Comparator:** Flucortin ointment 0.75%, twice daily (assumed moderate potency) (n=31)	**Severity:** Disease duration – mean 7.7 years (range 0.1 to 31). **Age:** adults 18-74 years (mean 33.6) **Sample size:** 67 participants			**<u>Adverse reactions</u>** **Prednicarbate:** 0/36 patients (0%) **Flucortin:** 2/31 patients (6.5%) *(Difference between groups: p = 0.16 [a])*
Mild potency topical corticosteroid versus another mild potency topical corticosteroid						
Lucky 1997 [96] ***(Callen 2007 [24]; Hoare 2000 [19]; Wood Heickman 2018 [9])***	RCT *(4 weeks treatment)* *(Moher 1995 quality checklist: method and concealment of randomisation unclear, open label, five dropouts, no ITT [19])*	**Intervention:** Desonide 0.05% ointment, twice per day (mild potency) **Comparator:** Hydrocortisone 2.5% ointment, twice per day (mild potency)	**Severity:** not specified in the review **Age:** children (mean or median is 4.7 years) **Sample size:** 20 participants		**<u>HPA axis suppression</u>** Normal in both groups (measured using ACTH stimulation testing, measuring serum cortisol levels)	
Jorizzo 1995 [97] ***(Siegfried 2016 [71]; Froeschl 2007 [98])***	RCT *(25 weeks: 5 weeks of treatment, 20 weeks follow up)* *(Moher 1995 quality checklist: method and concealment of randomisation unclear, investigator blind, two dropouts/withdrawals, no ITT [19])*	**Intervention:** 0.05% desonide twice daily (n=16) (mild potency) **Comparator:** 1% hydrocortisone ointment twice daily (n=20) (mild potency)	**Severity:** mild to moderate **Age:** children 5 years and under **Sample size:** 36 participants	**<u>Skin thinning</u>** No cases - measured by a magnifying lamp		

How safe are topical corticosteroids compared to Chinese herbal medicine?						
Study ID ***(Systematic review*)***	**Study design and study duration** ***(Quality assessment)***	**Intervention and comparator**	**Participants**	**Cutaneous adverse events**	**Systemic adverse events**	**Unspecified adverse events**
Very potent topical corticosteroids						
Huang 2010 [99] ***(Gu 2013 [100]; Gu 2014 [101])***	RCT *(2 weeks treatment, followed up for 12 weeks after)* *(Cochrane risk of bias tool: low risk of selection bias (random sequence generation), and other biases. Unclear risk of selection (allocation concealment), detection and attrition bias. High risk of performance and reporting bias. [100, 101]*	**Intervention:** Clobetasol propionate ointment, 3 times daily (n=97) **Comparator:** Chushi Zhiyang ointment, 3 times daily (n=98)	**Severity:** not specified in the review **Age:** children and adults, 3 months to 22 years **Sample size:** 195 participants	**Cutaneous adverse events** **Clobetasol:** 5/97 participants (5%) **Chinese herbal medicine:** 0/98 participants (0%) *(Difference between groups: p=0.10 [a, e])* The five events were pigmentation (unclear if hyper- or hypo-)		
Potent topical corticosteroids						
Chen 2011 [102] ***(Gu 2013 [100]; Gu 2014 [101])***	RCT *(2 weeks treatment)* *(Cochrane risk of bias tool: unclear risk of selection, detection, attrition, reporting and other bias. High risk of performance bias [100, 101])*	**Intervention:** Mometasone furoate cream, once daily (n=50) **Comparator:** Huanglian Qingdai ointment, 2 to 3 times daily (n=50)	**Severity:** not specified in the review **Age:** children 58 days to 2 years **Sample size:** 100 participants	**Cutaneous adverse events** **Mometasone:** 6/50 participants (12%) **Chinese herbal medicine:** 0/50 participants (0%) *(Difference between groups: p=0.08 [a, f])* Minor adverse events such as burning, dryness and scaling of the skin were reported in the TCS groups		
Dong 2012 [103] ***(Gu 2014 [101])***	RCT *(2 weeks treatment)* *(Cochrane risk of bias tool: unclear risk of selection, detection, attrition, and reporting bias. High risk of*	**Intervention:** Hydrocortisone butyrate cream, twice daily (n=47) **Comparator:** Jingfang mixture solution, twice daily (n=48)	**Severity:** not specified in the review **Age:** children 0.5 to 5.5 years **Sample size:** 95 participants	Minor adverse events such as burning, dryness and scaling of the skin were reported in the TCS groups. *(No numerical data provided in the review)*		

	performance bias. Low risk of other biases. [101])					
Xu 2012 [104] ***(Gu 2014 [101])***	RCT *(2 weeks treatment)* *(Cochrane risk of bias tool: unclear risk of selection, detection, attrition, and reporting bias. High risk of performance and other biases. [101])*	**Intervention:** Triamcinolone acetonide acetate cream, twice daily (n=51) **Comparator:** Kouqiang Xiaoyan powder, twice daily (n=53)	**Severity:** not specified in the review **Age:** children 35 days to 2 years **Sample size:** 104 participants			No adverse events in either group
How safe is more frequent topical corticosteroid application compared with once daily application?						
Study ID *(Systematic review*)*	**Study design and study duration *(Quality assessment)***	**Intervention and comparator**	**Participants**	**Cutaneous adverse events**	**Systemic adverse events**	**Unspecified adverse events**
Very potent topical corticosteroid						
Schlessinger 2006 [105] ***(Nankervis 2017 [3]; Wood Heickman 2018 [9])***	Open label RCT *(2 weeks treatment)* *(Cochrane risk of bias tool: unclear risk of selection bias, high risk from no blinding. [3])*	**Intervention:** fluocinonide cream 0.1% applied once daily (n=63) **Comparator:** fluocinonide cream 0.1% applied twice daily (n=63)	**Severity:** not specified in the review **Age:** children, aged 12 to <18 years (cohort 1); 6 to <12 years (cohort 2); 2 to <6 years (cohort 3); and 3 months to <2 years (cohort 4). **Sample size:** 126 participants		**<u>HPA axis suppression</u>** **Once daily**: 0/63 (0%) **Twice daily**: 3/63 (4.8%) *(Difference between groups: P=0.19[a])* (measured using ACTH stimulation testing, measuring serum cortisol levels) After TCS discontinuation, children with biochemical adrenal insufficiency had complete resolution at retesting.	
Potent topical corticosteroids						
Bleehen 1995 [106] ***(Green 2004 [107])***	RCT *(4 weeks treatment))* *(Quality using NHS CRD criteria: method for randomisation/allocation concealment unknown, adequate blinding, and ITT used. [107])* *(Moher 1995 quality checklist: method and*	**Intervention:** Fluticasone propionate 0.05% cream once daily (plus vehicle once daily for blinding) (n=137) **Comparator:** Fluticasone propionate 0.05% cream twice daily (n=133)	**Severity:** at least moderate severity **Age:** children and adults **Sample size:** 270 participants			**<u>Number of events possibility, probably or almost certainly related to study medication</u>** **Once daily:** 26 events **Twice daily**: 24 events (most were skin disorders)

	concealment of randomisation unclear, Probably investigator blinded but unclear, ITT analysis, [19])					
GSK report 1995 [108] ***(Green 2004 [107])***	RCT *(4 weeks treatment)* *(Quality using NHS CRD criteria: adequate method of randomisation /allocation concealment, adequate blinding, and ITT used. [107])*	**Intervention:** Fluticasone propionate 0.005% ointment once daily and placebo only daily (n=123) **Comparator:** Fluticasone propionate 0.005% ointment twice daily (n=122)	**Severity:** at least moderate severity **Age:** children and adults **Sample size:** 245 participants			**Number of adverse events possibly related to medication** **Once daily:** 6 events **Twice daily**: 8 events **Number of adverse events probably related to medication** **Once daily:** 9 events **Twice daily:** 3 events **Number of adverse events almost certain related to medication** **Once daily:** 6 events **Twice daily:** 3 events (Mainly included skin related disorders including exacerbation of eczema, pruritus and redness of skin)
Koopmans 1995 [109] ***(Green 2004 [107])***	RCT *(4 weeks treatment))* *(Quality using NHS CRD criteria: method for randomisation /allocation concealment unknown, partial blinding, and no ITT used. [107])* *(Moher 1995 quality checklist: method and concealment of randomisation unclear, double blinded, one dropout, no ITT analysis, [19])*	**Intervention:** Locoid lipocream (0.1% hydrocortisone 17-butyrate) once daily and locobase once daily (n=75) **Comparator:** Locoid lipocream twice daily (n=75)	**Severity:** not specified in the review **Age:** children aged over 12 years and adults **Sample size:** 150 participants	**Folliculitis in all skin areas after 1 week of treatment – treatment stopped** **Once daily:** 1/75 participants (1.3%) **Twice daily:** 0/75 participants (0%) *(Difference between groups: p = 0.50[a])* **Folliculitis - treatment continued** **Once daily:** 0/75 participants (0%) **Twice daily:** 4/75 participants (5.3%) *(Difference between groups: p = 0.14[a])* **Burning, itching and stinging sensations – treatment continued** **Once daily:** 3/75 participants (4%)		

				Twice daily: 0/75 participants (0%) *(Difference between groups: p = 0.20[a])*		
Tharp 1996 [110] ***(Green 2004 [107])***	RCT *(4 weeks treatment)* *(Quality using NHS CRD criteria: method for randomisation /allocation concealment unknown, adequate blinding, and no ITT used. [107])*	**Intervention:** Fluticasone propionate cream 0.05% once daily and vehicle once daily (n=77) **Comparator:** Fluticasone propionate cream 0.05% twice daily (n=77)	**Severity:** moderate to severe **Age:** children over 12 years and adults **Sample size:** 154 participants	**Burning** **Once daily**: 2/77 participants (3%) **Twice daily:** 0/77 participants (0%) *(Difference between groups: p = 0.30[a])* **Dryness** **Once daily:** 2/77 participants (3%) **Twice daily:** 0/77 participants (0%) *(Difference between groups: p = 0.30[a])* **Pruritus** **Once daily:** 0/77 participants (0%) **Twice daily**: 1/77 participants (1%) *(Difference between groups: p = 0.50[a])* **Erythema** **Once daily:** 0/77 participants (0%) **Twice daily:** 0/77 participants(0%) **Stinging** **Once daily:** 0/77 participants (0%) **Twice daily:** 1/77 participants (1%) *(Difference between groups: p = 0.50[a])* **Irritation** **Once daily:** 0/77 participants (0%) **Twice daily:** 1/77 participants (1%)		None of adverse events were serious or unexpected

				(Difference between groups: p = 0.50[a])		
Hoybye 1991 [111] ***(Green 2004 [107])***	RCT *((3 weeks treatment)* *(Quality using NHS CRD criteria: method for randomisation /allocation concealment unknown, partial or inadequate blinding, and no ITT used. [107])* *(Moher 1995 quality checklist: method and concealment of randomisation unclear, single blind, ten dropouts/withdrawals, no ITT analysis, [19])*	**Intervention:** Mometasone furoate in fatty cream base (Elocon) once daily (n=49) **Comparator:** Hydrocortisone 17-butyrate in fatty cream base (Locoid) twice daily (n=45)	**Severity:** severity score at least 4.5/9 **Age:** adults (age 18 to 70) **Sample size:** 94 participants	**Treatment related side effects** Were only a few and similar in both groups. They included stinging, burning, itching, dryness, acne, folliculitis, and hair growth. **Skin thinning** No evidence		
Berth-Jones 2003 [112] ***(Green 2004 [107])*** (This study is also included in the "Topical corticosteroids used proactively to prevent flares", as there is a second phase of the study when participants who have gained control of eczema are randomised to proactive treatment with topical corticosteroid or vehicle. This section only	RCT (four arms) *(4 weeks treatment)* *(Quality using NHS CRD criteria: adequate randomisation /allocation concealment, partial blinding, and ITT used. [107])*	**Intervention:** Fluticasone propionate cream 0.05% once daily N=95 **Intervention:** Fluticasone propionate ointment 0.005% once daily N=100 **Comparator:** Fluticasone propionate cream 0.05% twice daily N=91 **Comparator:** Fluticasone propionate ointment 0.005% twice daily N=90	**Severity:** moderate to severe **Age:** children and adults (12-65 years) **Sample size:** 376 participants	**Telangiectasia** **Once daily cream**: 0/95 participants (0%) **Twice daily cream:** 1/91 participants (1%) *(Difference between groups: p = 0.48[a])* **Once daily ointment:** 1/100 participants (1%) **Twice daily ointment:** 0/90 participants (0%) *(Difference between groups: p = 0.54[a])* **Striae** **Once daily cream:** 0/95 participants (0%) **Twice daily cream:** 0/91 participants (0%) *(Difference between groups: n/a)* **Once daily ointment:** 1/100 participants (1%) **Twice daily ointment**: 0/90 participants (0%)		

includes safety data from the induction of remission phase).				*(Difference between groups: p = 0.54[a])* For the three events listed above: two of these patients had a previous history of skin changes, and therefore only one report was newly observed (group not specified in the review).		
Marchesi 1994 [113] ***(Green 2004 [107])***	RCT *(3 weeks treatment))* *(Quality using NHS CRD criteria: method for randomisation /allocation concealment unknown, partial blinding, and no ITT used. [107])* *(Moher 1995 quality checklist: method and concealment of randomisation unclear, third-party blind evaluator, no dropouts/withdrawals [19])*	**Intervention:** Mometasone furoate ointment 0.1% once daily (n=30) **Comparator:** Betamethasone dipropionate ointment 0.05% twice daily (n=30)	**Severity:** at least moderate severity **Age:** adults **Sample size:** 60 participants	**Telangiectasia of mild severity in last 2 weeks** **Once daily:** 4/30 participants (13.3%) **Twice daily:** 5/30 participants (16.7%) *(Difference between groups: p = 0.72[a])* **Possible skin thinning (*"Loss of skin marks and reduced elasticity"*)** **Once daily:** 0/30 participants (0%) **Twice daily:** 1/30 participants (3.3%) *(Difference between groups: p = 0.50[a])* **Local application site reactions** Did not occur	**Systemic reactions** None – all patients checked for blood test and value varied within a very narrow range.	
Moderate potency topical corticosteroids						
Richelli 1990 [114] ***(Green 2004 [107])***	RCT (one week treatment *(Quality using NHS CRD criteria: method for randomisation /allocation concealment unknown, inadequate blinding, and no ITT used. [107])* *(Moher 1995 quality checklist: method and concealment of*	**Intervention:** Clobetasone 17-butyrate 0.05% lotion once daily at 9pm (n=9) **Comparator:** Clobetasone 17-butyrate 0.05% lotion twice daily at 8am and 3pm (n=13) **Comparator:** Clobetasone 17-butyrate 0.05% lotion twice daily at 3pm and 8pm (n=8)	**Severity:** not specified in the review **Age:** children **Sample size:** 30 participants		**HPA axis suppression** No significant difference in serum cortisol and ACTH levels before and after TCS administration in any of the three groups, or any differences between groups	Adverse effects not reported

	randomisation unclear, blinding unclear, ITT unclear [19])					
How safe are topical corticosteroids when used proactively to prevent flares ("weekend therapy")?						
Study ID *(Systematic review*)*	**Study design and study duration *(Quality assessment)***	**Intervention and comparator**	**Participants**	**Cutaneous adverse events**	**Systemic adverse events**	**Unspecified adverse events**
Potent topical corticosteroids versus vehicle						
Berth-Jones 2003 [112] ***(Schmitt 2011 [115]; Tang 2014 [88])*** (This study is also included under the comparison "Topical corticosteroids applied once a day compared with more frequent application" – where the induction of remission part of the study is included).	RCT *(16 weeks maintenance)* *(Cochrane risk of bias tool: low risk of selection (sequence generation), attrition and other biases, Unclear risk of selection (allocation concealment), bias from blinding and reporting bias. [115])*	**Intervention:** Fluticasone propionate 0.005% ointment on two consecutive days per week, once daily (n=68) **Intervention:** Fluticasone propionate 0.05% cream on two consecutive days per week, once daily (n=70) **Comparator:** Vehicle cream or ointment (n=84) **Comparator:** Vehicle ointment (n=73)	**Severity:** moderate to severe **Age:** 12 to 65 years **Sample size (maintenance phase):** 295 participants	**Skin thinning** No new visual signs observed in either group during maintenance phase		
Glazenburg 2009 [116] ***(Schmitt 2011 [115]; Tang 2014 [88])***	RCT *(16 weeks maintenance)* *(Cochrane risk of bias tool: low risk of selection (sequence generation), and attrition bias. Unclear risk of selection (allocation concealment), bias from blinding, reporting and other biases. [115])*	**Intervention:** Fluticasone propionate 0.005% ointment (two consecutive days per week, once daily) (n=39) **Comparator:** Vehicle (n=36)	**Severity:** moderate to severe **Age:** children 4-10 years **Sample size (maintenance phase):** 75 participants	**Skin thinning** No evidence in either group **Adverse events related to treatment (cutaneous)** **Fluticasone:** 2 events (flexural hyperpigmentation, folliculitis, transient telangiectasia) (n=39) **Vehicle:** 1 event (no further details reported) (n=36) *(Difference between groups: p=0.61[a])*	**Adrenal suppression** No evidence in either group (measured by assessment of urinary overnight cortisol/creatinine ratios) **Cancer** No cases in either group	

Hanifin 2002 [117] ***(Schmitt 2011 [115])*** ***(Fishbein 2019 [16])***	RCT *(20 weeks maintenance)* *(Cochrane risk of bias tool: low risk of attrition bias. Unclear risk of selection, bias from blinding and reporting bias. High risk of other biases (noncompliance) [115])*	**Intervention:** Fluticasone propionate 0.05% cream (once daily 4 days per week for 4 weeks, then once daily 2 days per week for 16 weeks) (n=229) **Comparator:** Vehicle (n=119)	**Severity:** moderate to severe **Age:** children and adults, 3 months to 65 years **Sample size (maintenance phase):** 348 participants	**Adverse events related to treatment** **Fluticasone:** 1/229 (one case of acne) (0.4%) **Vehicle:** 0/119 (0%) *(Difference between groups: p=0.78[a])* **Skin thinning** No evidence (by visual skin assessment)	**Possible adrenal suppression** **Fluticasone:** 2/44* children (4.5%) **Vehicle:** no evidence of adrenal suppression *(measured by cosynthropin stimulation test)* *One participant received 345 days of treatment and had a cortisol stimulation level after treatment of 17 ug/dL (normal was >=18 ug/dL). The other participant was treated for 280 days and had a cortisol stimulation level of 9 ug/dL. No follow up testing. **Cancer** No cases	
Van der Meer 1999 [118] ***(Schmitt 2011 [115])***	RCT *(16 weeks maintenance)* *(Cochrane risk of bias tool: low risk of attrition, and other biases. Unclear risk of selection, bias from blinding and reporting bias. [115])* *((Moher 1995 quality checklist: method and concealment of randomisation unclear, double blinded, 17 withdrawals/dropouts, no ITT, only data up to first relapse analysed, [19])*	**Intervention:** Fluticasone propionate 0.005% ointment (2 consecutive days per week, once daily) (n=23) **Comparator:** Vehicle (n=31)	**Severity:** moderate to severe **Age:** children and adults, aged 15-50 years **Sample size (maintenance phase):** 54 participants	**Skin thinning** No evidence	**Adrenal suppression** No change in geometric mean cortisol levels at baseline and end of maintenance **Cancer** No cases	
Peserico 2008 [119] ***(Schmitt 2011 [115])***	RCT *(16 weeks maintenance)* *(Cochrane risk of bias tool: high risk of selection bias (sequence generation). Low risk of attrition bias and bias from blinding. Unclear*	**Intervention:** Prednisolone aceponate 0.1% cream (two consecutive days per week, once daily) (n=112) **Comparator:** Vehicle (n=108)	**Severity:** IGA≥ moderate **Age:** children ≥12 years and adults **Sample size (maintenance**	**Skin thinning** No evidence	**Cancer** No cases.	**Adverse events related to treatment** Zero in both groups

	risk of selection (allocation concealment) reporting and other biases. [115]*)*		**phase):** 221 participants			
How safe are topical corticosteroids used under occlusion?						
Study ID ***(Systematic review*)***	**Study design and study duration** ***(Quality assessment)***	**Intervention and comparator**	**Participants**	**Cutaneous adverse events**	**Systemic adverse events**	**Unspecified adverse events**
Very potent topical corticosteroid						
Volden 1992 [120] ***(Braham 2010*** [121]***)***	Prospective (observational) *(8-18 days treatment)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** Dry occlusion with clobetasol propionate lotion under dry occlusion (weekly) (n=48) **Comparator:** No comparator	**Severity:** therapy resistant atopic eczema **Age:** adults **Sample size:** 48 participants	**Mild folliculitis** 2/48 participants (4%) **Skin thinning** None		
Potent topical corticosteroids						
Janmohamed 2014 [122] ***(Van Zuuren 2017*** [12]***)***	RCT *(4 weeks treatment)* *(Cochrane risk of bias tool: low risk of selection (sequence generation), attrition, reporting and other biases. Unclear risk of selection (allocation concealment), performance and detection bias.* [12]*)*	**Intervention:** wet wrap therapy with diluted mometasone furoate 0.1% ointment (n=19) **Comparator:** 20% petrolatum in cetomacrogol combined with wet wrap (n=20)	**Severity:** severe **Age:** children 6 months to 10 years (mean age 3.4 years) **Sample size:** 39 participants	**Folliculitis** **Mometasone under wet wrap:** 9/19 (47%) **Emollient under wet wrap:** 2/20 (10%) *(Difference between groups: p = 0.03*[a]*)* **Severe folliculitis** **Mometasone under wet wrap:** 1/19 (5.2%) **Emollient under wet wrap:** 0/20 (0%) *(Difference between groups: p = 0.47*)* **Secondary infected eczema** **Mometasone under wet wrap:** 0/19 (0%) **Emollient under wet wrap**: 2/20 (10%) *(Difference between groups: p= 0.30*[a]*)* **Beginning of decubitus** **Mometasone under wet wrap:** 0/19 (%)		

				Emollient under wet wrap: 2/20 (10%) *(Difference between groups: p = 0.30[a])* **<u>Decubitus</u>** **Mometasone under wet wrap:** 2/19 (11%) **Emollient under wet wrap:** 1/20 (5%) *(Difference between groups: p = 0.53[a])*		
Schnopp 2002 [123] ***(Braham 2010 [121])***	RCT, within-participant *(5 days treatment)* *(Cochrane risk of bias tool: unclear risk of selection bias, unclear risk from blinding. [3])*	**Intervention:** wet wrap therapy with mometasone furoate 0.1%, twice daily **Comparator:** wet wrap therapy with vehicle	**Severity:** exacerbated atopic eczema **Age:** children aged 2 to 17 years (mean 7.2 years) **Sample size:** 20 participants	**<u>Clinical skin infections</u>** None in either group		
McGowan 2003 [124] ***(Devillers 2006 [125])***	Prospective (observational) *(Up to 14 days treatment)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** wet wrap therapy with diluted beclomethasone dipropionate, once daily (n=8) **Comparator:** No comparator	**Severity:** not specified in the review **Age:** children age 3.3 to 8.8 years **Sample size:** 8 participants		**<u>Short term growth and bone turnover</u>** No significant differences found between outcomes before and during a median treatment period of 12 weeks (range 2-18). *(assessed safety with knemometry and urinary deoxypyridinoline crosslink excretion and early morning serum cortisol).*	
Wolkerstorfer 2000 [126] ***(Braham 2010 [121])*** ***(Fishbein 2019 [16])***	Prospective, side to side (observational) *(1 week treatment)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** wet wrap therapy with 10-50% dilution fluticasone propionate 0.05% cream (daily) **Comparator:** emollient (only 2 participants) or no comparator	**Severity:** severe **Age:** children 5 months to 13 years **Sample size:** 18 participants	**<u>URI and/or folliculitis</u>** **Fluticasone:** one third of participants **<u>Furunculosis</u>** **Fluticasone:** one case **<u>Generalized folliculitis</u>** One case in both emollient controls **<u>Skin thinning</u>** No cases	**<u>HPA axis suppression</u>** "Nearly all" had decreased cortisol, 3 children were HPA suppressed (from Braham 2010 review). Two patients having a 9am serum cortisol < 0.2 umol/L (0.09 and 0.03) after treatment for 7 days. Those participants used 957 ug/m^2 and 1125 ug/m^2 of steroid cream. There was no follow up	

					testing (from Fishbein 2019 review).	
Tang 2000 [127] ***(Braham 2010 [121])***	Prospective (observational) *("Few days" treatment)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** wet wrap therapy with 10% dilution mometasone furoate 0.1% (daily for 2 to 3 hours) (n=10) **Comparator:** No comparator	**Severity:** review only reports 'facial eczema flare' **Age:** children (mean 8.4 years) **Sample size:** 10 participants	**Skin thinning** None **Infections** None		
Goodyear 1991 [128] ***(Braham 2010 [121])***	Prospective (observational) *(2 to 5 days treatment)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** wet wrap therapy with 25% dilution betamethasone or hydrocortisone 1%, twice daily (potent or mild potency) (n=30) **Comparator:** No comparator	**Severity:** acute erythrodermic eczema **Age:** children aged 9 months to 2 years (mean 5.5 years) **Sample size:** 30 participants	**Bacterial infections** Some during follow up at home	**HPA axis suppression** Transient low morning cortisol. During the follow up at home some adrenal suppression.	
Mallon 1994 [129] ***(Braham 2010 [121])***	Prospective (observational) *(up to 5 days treatment)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** wet wrap therapy with 10% dilution betamethasone 0.1% cream or hydrocortisone 0.5% cream(daily) (potent or mild potency) (n=21) **Comparator:** No comparator	**Severity:** chronic severe eczema **Age:** children aged 4 months to 10 years (5.1 years) **Sample size:** 21 participants	No infections.		
Devillers 2002 [130] ***(Braham 2010 [121])***	Retrospective side to side (observational) *(1 week treatment)* *Risk of bias not assessed in any of the included systematic reviews.*	**Intervention:** wet wrap therapy with **d**iluted fluticasone propionate 0.05% (daily re-wet every 2 to3 hours) (n=26) **Comparator:** No comparator	**Severity:** refractory atopic eczema **Age:** children (mean 3 years), adults (mean 30 years) **Sample size:** 26 participants (14 children, 12 adults)	**Infections** 38% (n=10) had localized folliculitis, impetigo, pseudomonas, cellulitis, or purulent conjunctitivitis **Skin thinning** One case of striae in a patient taking inhaled steroids.	**HPA axis suppression** Transient low morning cortisol, 12.5% with HPA suppression	
Moderate potency topical corticosteroids						
Foelster-Holst 2006 [131]	Within-participant RCT *(48 to 72 hours treatment)*	**Intervention:** wet wrap therapy with prednicarbate ointment	**Severity:** local SCORAD >10, severe	Zero adverse events in either group. Did not observe severe cutaneous events.	Did not observe systemic events such as growth retardation or HPA suppression – but these	

(Gonzalez-Lopez 2017 [132])	*(Cochrane risk of bias tool: unclear risk of selection and performance bias. High risk of performance bias. Unclear risk of attrition, reporting and other biases. [132])* *(Cochrane risk of bias tool: unclear risk of selection bias, high risk from no blinding. [3])*	**Comparator:** Prednicarbate ointment	**Age:** children and adults, aged 6-63 years **Sample size: 24** participants		events were not actively investigated.	
Mild potency topical corticosteroid						
Beattie 2004 [133] ***(Gonzalez-Lopez 2017 [132])***	RCT *(2 weeks treatment)* *(Cochrane risk of bias tool: low risk of selection, reporting and other biases. High risk of performance and attrition bias. Unclear risk of detection bias. Gonzalez-Lopez 2017)* *(Cochrane risk of bias tool: low risk of selection bias (sequence generation), unclear risk of selection bias (allocation concealment), unclear risk from blinding. [3])*	**Intervention:** wet wrap therapy with hydrocortisone 1% twice daily then overnight the second week(n=10) **Comparator:** Hydrocortisone 1% twice daily then daily (n=9)	**Severity:** moderate **Age:** children < 5 years **Sample size:** 19 participants	**Cutaneous adverse events** **Wet wrap therapy with hydrocortisone:** 2/10 participants (20%) (2 events were folliculitis, one child withdrew) **Hydrocortisone only:** 0/9 participants (0%) *(Difference between groups: (p=0.31 [a])* Did not observe severe cutaneous events.	Did not observe systemic such as growth retardation or HPA suppression – but these events were not actively investigated.	
Hindley 2006 [134] ***(Gonzalez-Lopez 2017 [132])***	RCT *(4 weeks – not clear if treatment given for whole 4 weeks)* *(Cochrane risk of bias tool: low risk of selection (random sequence generation) and reporting bias. Unclear risk of selection (allocation concealment),*	**Intervention:** wet wrap therapy with hydrocortisone 1% for 24 hours – could be reduced to 12 hours per day after first week (n=28) **Comparator:** Hydrocortisone 1% twice day (n=22)	**Severity:** SCORAD >15, moderate to severe **Age:** children 3 months to 5 years **Sample size:** 50 participants	**Cutaneous adverse events** **Wet wrap therapy with hydrocortisone:** 5/28 participants (18%) (five cases of infected eczema) **Hydrocortisone only:** 0/22 participants (0%) *(Difference between groups: p = 0.14 [a])*	Did not observe systemic events such as growth retardation or HPA suppression – but these events were not actively investigated.	

	detection and other biases. High risk of performance and attrition bias. [132]) *(Cochrane risk of bias tool: unclear risk of selection bias, low risk from blinding. [3])*			Did not observe severe cutaneous events.		

Footnotes:

*This column refers to the systematic review in which the safety data was extract from. The trial may have also been included in other systematic reviews, but no additional safety data was reported.

Abbreviations: RCT = randomised controlled trial; TCS = topical corticosteroids; TCI = topical calcineurin inhibitors; HPA = hypothalamic pituitary adrenal, WWT = wet wrap therapy; RR = risk ratio; OR: odds ratios; 95% CI = 95% confidence interval; CHM = Chinese herbal medicine; IPA = Investigator's Global Assessment; BSA = Body Surface Area

[a] P value calculated by review authors using RevMan software.

[b] The P value calculated from Fisher's Exact Test was significant: 0.0298 (but in the overview, this study is included in a meta-analysis)

[c] The P value calculated from Fisher's Exact Test was significant: 0.0298 (but in the overview, this study is included in a meta-analysis)

[d] The P value calculated from Fisher's Exact Test was significant: 0.0352 (but in the overview, this study is included in a meta-analysis)

[e] The P value calculated from Fisher's Exact Test was significant: 0.0289 (but in the overview, this study is included in a meta-analysis)

[f] The P value calculated from Fisher's Exact Test was significant: 0.0267 (but in the overview, this study is included in a meta-analysis)

Where studies include "diluted" topical corticosteroids and we aren't sure how this affects the potency, we have put the topical corticosteroids in the potency classification based on the undiluted version.

The terms skin atrophy and skin thinning were both used in the included reviews – for consistently we have used skin thinning throughout.

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